PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Rajagopalan et al.
Serial No.:	09/898,809
Filed:	July 3, 2001
Group Art Unit:	1624
Confirmation No:	5120
Examiner:	McKenzie
Title:	**DYE-SULFENATES FOR DUAL PHOTOTHERAPY**
Our Ref. No.:	MRD-63

Cincinnati, Ohio 45202 May 9, 2005

Mail Stop AMENDMENT
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF BERNARD F. ERLANGER, Ph.D. PURSUANT TO 37 C.F.R. §1.132

Sir:

I, Bernard F. Erlanger, declare as follows:

1. I hold the rank of Professor and have been on the faculty in the Department of Microbiology at Columbia University for 48 years. My Ph.D. is in Biochemistry and was awarded from Columbia University. My research encompasses photobiology, photochemistry, immunology, and receptor biochemistry including research in receptor binding compounds, and I have been an invited speaker at professional symposia on these topics. I am an inventor on eight issued patents,

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including U.S. Patent No. 4,818,684 entitled Auto-Anti-Idiotypic Monoclonal Antibodies to Steroid Receptors and Uses Thereof; steroid receptor binding molecules are included in one embodiment of the instant application. I have published over 250 articles in the peer-reviewed scientific literature. I was a post-doctoral research advisor to Dr. Rajagopalan, a named inventor of the instant application, and have kept in contact with him on an intermittent social basis. My research, teaching, publication, and participation in scientific conferences brings me into contact with others skilled in the photobiology, photochemistry, and receptor binding arts, which are included in the instant application. My curriculum vitae is attached.

2. I have read the specification of U.S. Patent Application Serial No. 09/898,809 as it was filed with the U.S. Patent and Trademark Office, the claims currently pending, and the February 9, 2005 Office Action.

3. I understand that the Examiner holds the opinion that the specification does not disclose sufficient information to put the public in possession of the invention, which is referred to as the "written description" requirement in the Office Action. I understand that a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventors had possession of the claimed invention. I understand that possession can be shown with words, structures, figures, diagrams, and structural chemical formulas. I understand that actual reduction to practice is not required.

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4. I understand that the Examiner holds the opinion that the specification does not enable those skilled in the art to make and use the invention, as it is claimed, without undue experimentation, which is referred to as the "enablement" requirement in the Office Action. I understand its purpose is to ensure that the invention is communicated to the interested public in a meaningful way, and that the specification must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. I understand that factors to be considered include the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventors, the existence of working examples although I understand that working examples are not required, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

5. I understand that the Examiner holds the opinion that the claims are not sufficiently definite because one skilled in the art would not know identities of the claimed receptor binding compounds.

6. The instant application claims a method of performing a photosensitizing procedure in which the sulfenate, as part of the formula

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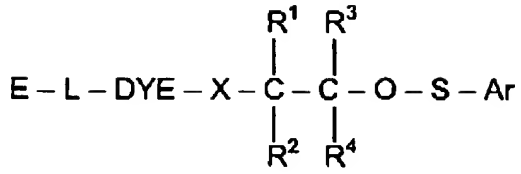

is administered to a target tissue, and then the target tissue is exposed to light at a wavelength, power, and fluence rate to cause necrosis or apoptosis of the target tissue.

7. In my opinion, such a method is disclosed in the specification in sufficient detail to allow me to reasonably conclude that the inventors had possession of this invention, and that one skilled in the art would be able to make and use this invention without undue experimentation, and that the claims are sufficiently definite to allow one skilled the art to determine what is claimed.

8. Based on the documents that I reviewed, I was asked if and how I could determine each of the following:

- the relationship between the structure of the sulfenate and its function,
- selection of the targeting group and attachment to the sulfenate,
- what compounds or portions of compounds to select as a binding molecule for each of the following receptors: somatostatin, heat sensitive bacterioendotoxin, neurotensin, bombesin, cholecystekinin, steroid, and carbohydrate
- how I would carry out the method that is claimed.

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I understand that the Examiner finds the application does not describe and/or enable the above issues, and for this reason the Examiner rejects the application.

9. I respectfully disagree with the Examiner. It is my opinion that, based on the patent application as filed, I am able to address each of the above issues as I subsequently explain. It is my opinion that doing so requires a level of experimentation that is reasonable for one skilled in this art; it is not "undue".

10. I would first search the literature to determine the structures of compounds that bind to each of the above receptors. For example, in searching for "steroid receptor binding molecules", as the claims require, I attach page 563 of Fundamentals of Clinical Chemistry, 3rd Edition, Tietz (Ed), showing structures of steroids.

11. I would then identify the functional group(s) in the compound that could be modified to link the compound to the claimed formula without destroying the ability of the compound to bind to the receptor (or as described at page 563, a group apart from the circled "site of chemical changes"). That is, I would look to a group apart from the actual site binding site to the claimed formula. These functional groups are known to one skilled in the art and include carboxyl, hydroxyl, amino, and keto groups, to name a few.

12. As one example, estradiol has the following formula (with ring designations A, B, C, and D shown):

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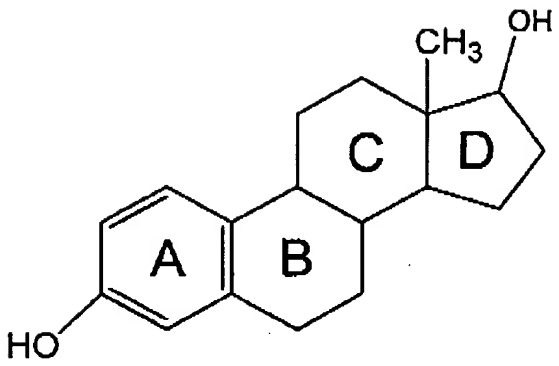

Estradiol is a steroid and hence binds to a respective steroid receptor; it is a "steroid receptor binding molecule", as the claims require. Because ring A in estradiol is involved with steroid activity, as indicated on attached page 563, I would not select ring A to link estradiol to the claimed formula. I instead would select a site apart from the active site to minimize interference with chemical activity of estradiol. Thus, I would look to ring D as a possible site of attaching estradiol as "E" to either "L" or "DYE" in the claimed formula. Ring D has a hydroxyl (-OH) group; this is a functional group that could be modified. I would esterify it by reaction with succinic anhydride. The result would be a hemisuccinate in which a carboxyl group (-COOH) is available for attachment to "L" or "DYE" in the claimed formula.

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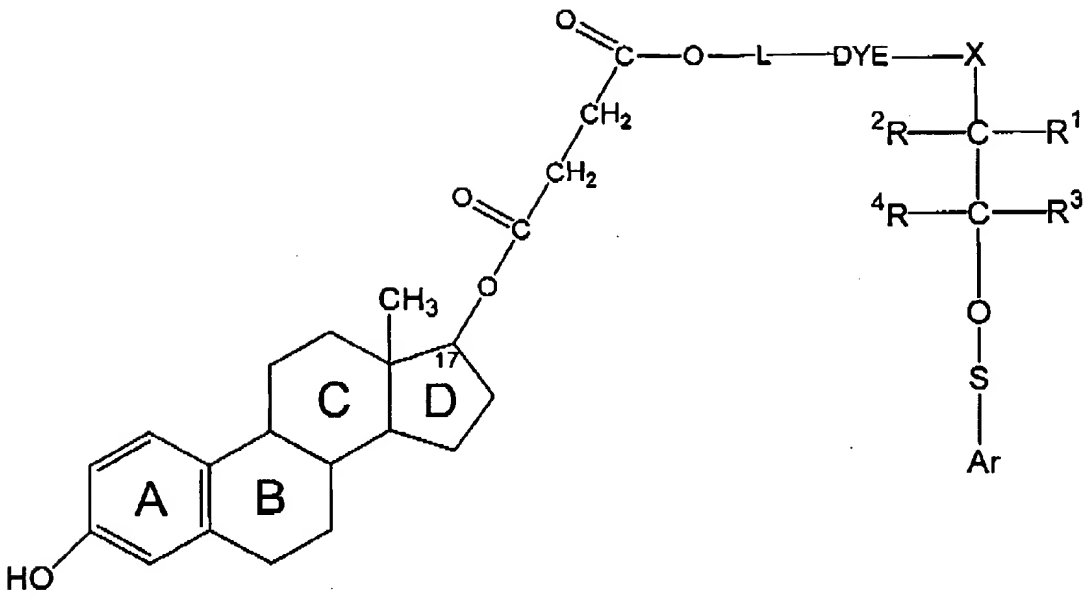
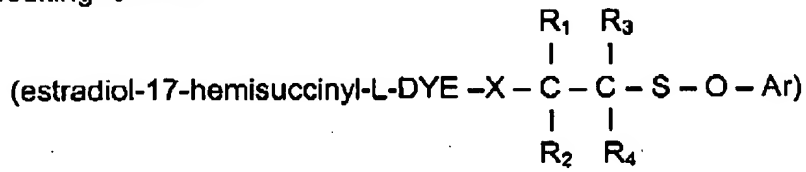


13. The resulting formula



could be administered to a target tissue in an animal an effective amount, as the claims require.

14. I disagree with the Examiner that structures of all molecules binding to the claimed receptors must be stated. This is simply not the case. As I have analyzed, knowledge of the target site, which the instant application provides (e.g., somatostatin receptor, a heat sensitive bacterioendotoxin receptor, a neurotensin receptor, a steroid receptor, etc.), allows one skilled in the art to

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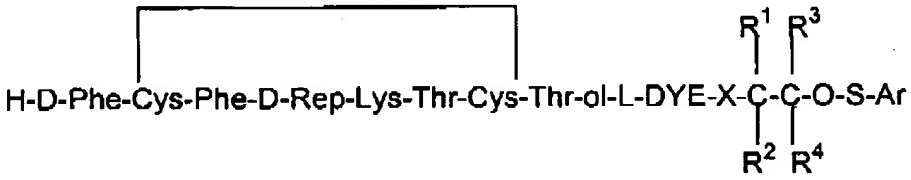
select a ligand for that target without undue experimentation. For example, it is known that the peptide octreotide is a somatostatin analogue and hence it binds to the somatostatin receptor. Thus, to target the claimed formula to a somatostatin receptor, one skilled in the art could attach octreotide as "E" to "L" or "DYE" in the claimed formula using, e.g., the -OH group of the terminal threonine. I would then use this group to attach octreotide to "L" or "DYE" in the claimed formula.



15. In my opinion, using the procedures I have indicated for steroid receptor binding compounds and somatostatin receptor binding compounds, one skilled in the art would be able to determine the identity of receptor binding compounds and devise appropriate functionalizations to include them in the claimed formula. Moreover, such determinations are routine and readily determined; it is my opinion they are not "undue experimentation".

16. The Examiner has also inaccurately defined the receptor targeting group "E". He states

> The Examiner understands that an epitope is a portion of a macromolecule chain capable of forming an antibody. Is "E" an antibody or only a short peptide segment from an antibody? If only macromolecules can be epitopes, then how can steroid hormones and amino acids be epitopes? (page 6, February 9, 2005 Office Action)

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This is inaccurate. An epitope generally refers to a portion of a macromolecule chain that is capable of being recognized by an antibody. In line with that generally accepted definition, the specification clearly teaches that "E" is a particular region of the molecule that is recognized by, and binds to, the target site (page 12, lines 17-18). In other words, "E" functions to locate the sulfenate at the target site (page 14, line 21). The Examiner's assertion that "E" is "capable of forming an antibody" is wholly unsupported by the description of "E" in the subject application. In contrast to the Examiner's statement, and based on my understanding of the application, "E" need not be a macromolecule and, indeed, can be a low molecular weight structure, such as a steroid, a carbohydrate, etc. which would bind to a steroid receptor, a carbohydrate receptor, etc. as required in the claims.

17. As a result of the Examiner's mischaracterization of an epitope, the Examiner's questions that follow his statement lack meaning. Indeed, steroids can be recognizable epitopes, because when they are attached to a carrier protein (e.g., bovine serum albumin) they can elicit steroid-specific antibodies. I have authored an article dealing with this issue, which I have attached in support of my assertion (The Preparation of Antigenic Hapten-Protein Conjugates: A Survey. Methods in Enzymology 70:85 (1980)).

18. I respectfully disagree with the Examiner that there is no correlation between the structure of the claimed formula and its function. The specification

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discloses that the sulfenate group is key to the photoactivating process. Free radicals are produced upon exposure to light of the proper wavelength. E is the group that binds to one of the claimed receptors and hence locates the formula at the desired site.

19. I respectfully disagree with the Examiner that the structures of all molecules fitting the claimed functional limitation of E are required. I would be able to "immediately envisage" the compounds fitting the description of E. E is selected for its ability to bind to the target in the affected tissue. Using the examples previously analyzed, I would select a steroid for E to target a tumor of the testis, because such a tumor would likely have a steroid receptor. I would select octreotide for E to target a somatostatin receptor; this is commercially available as Sandostatin® from Novartis as a medicinal preparation useful in the management of gastrointestinal endocrine tumors. I could also select bombesin to target the somatostatin receptor, this is a tetradecapeptide (Pyro-Glu Asn Arg Leu Gly Asn Gln Trp Ala Val Gly His Leu Met-amide) and also is commercially available (e.g., Alpha Diagnostics International, San Antonio TX). With respect to the other receptors, similar reasoning would hold.

20. Locating the claimed formula at the receptor so that the sulfenate can be photoactivated is required; the inventors are not claiming any particular binding property. Thus, I respectfully disagree with the Examiner's statement that "Since

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the binding affinities of molecules for receptors are dependent upon the conditions of the assay such information is crucial for determining which molecules are embraced by Applicants' claims".

21. In my opinion, binding affinities and assay conditions are not "crucial" for determining E for at least two reasons: (1) any binding that locates the sulfenate at the claimed receptors will suffice; and (2) one skilled in the art knows or can readily determine without undue experimentation which compounds will locate the sulfenate at the claimed receptors.

22. I further disagree with the Examiner's statement that "Nowhere do Applicants provide any assays that could be used to determine such binding" (page 6, February 6, 2005 Office Action). One skilled in the art would recognize RIAs and ELISAs as ways to demonstrate binding, e.g., a competitive assay with directed binding to the desired hapten-protein conjugate inhibited by E (the epitope as a small soluble molecule). I refer to my previously cited Methods in Enzymology paper; and also Engvall, Enzyme Immunoassays; Methods in Enzymology 70:419 (1980) (attached) as evidence that one skilled in the art would be aware of such assays.

23. Based on the teachings of the specification, I understand that E would serve to locate the active portion of the molecule to the "target" site to be treated. This target is a receptor for one of the compounds listed above. Thus, a

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compound that binds to one of these receptors would locate the sulfenate to the desired site. I can immediately envision which molecules would bind to each of these receptors, because such targeting is known to one skilled in this art. The selection, addition, and evaluation of such a targeting compound is not, in my opinion, "undue" experimentation because the identity, availability, affinity, avidity, testing, etc. of such receptor binding compounds are established in the art. In my opinion, any experimentation to formulate or enhance such targeting would certainly not be "undue", but instead would be encompassed by routine organic synthesis and/or receptor binding assays. For example, one skilled in the art would likely consider 1 μM for receptor affinity, but again this could be empirically determined without undue experimentation.

24. For at least the reasons I have set forth, I respectfully assert that one skilled in the art would be able to make the claimed invention without undue experimentation, and that the inventors were in possession of their invention at the time they filed the instant application.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the subject application or any patent issued thereon.

May 9 2005
Date

Bernard F. Erlanger, Ph.D.

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